Breast Cancer Multigene Testing Trends and Impact on Chemotherapy Use

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ABSTRACT

Objectives: A 21-gene test that predicts recurrence risk among women with hormone receptor positive (HR+), localized breast cancer was nationally recommended in 2007, but we know little about its subsequent impact. We evaluated: a) patient characteristics associated with test use, b) correlations between Recurrence Score (RS) and chemotherapy, and c) whether test introduction was associated with a reduction in chemotherapy use.

Study Design: Retrospective cohort study.

Methods: The Kaiser Permanente Northern California tumor registry and electronic health records from 2005 to 2012 were used to identify HR+, human epidermal growth factor receptor 2 negative, node-negative cancers. Analyses used logistic regression with propensity score matching and 2-level logistic regression.

Results: Of the 7004 patients who met guidelines for testing, 22% were tested and 26% had chemotherapy. Test use was more likely in younger women (for ages 40-49 years vs 50-64 years: odds ratio [OR], 1.22; 95% CI, 1.04-1.44), in women with tumors sized 1.0 to 2.0 cm versus >2 cm (OR, 1.20; 95% CI, 1.03-1.40), and in women from higher-income neighborhoods (for each $10,000 increase in area median income: OR, 1.05; 95% CI, 1.03-1.07). Among patients with low RS, 8% had chemotherapy versus 72% among patients with high RS (P <.01). In propensity score-matched analyses, testing was associated with an absolute reduction of 6.2% in the proportion of women receiving chemotherapy (95% CI, 2.9%-9.5%); the 2-level model showed a similar but nonsignificant (P = .14) association.

Conclusions: The 21-gene test is used in a minority of eligible patients in this integrated plan. Its use appears to be associated with a modest decrease in overall chemotherapy use.

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Genetic testing of tumor cells has the potential to revolutionize the care of patients with breast cancer and to accelerate the benefits of personalized medicine.[1] Several studies have observed that these tests have been incorporated into clinical practice and seem to influence chemotherapy decisions.[2-6] Recent US studies of claims data and the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data found that only 20% to 30% of eligible women were being tested, with the claims data study observing that reimbursement by insurers has increased slowly.[4,5] It is unknown whether acceptance and use of this test have been more complete in integrated, fully capitated systems where the costs of care are covered and decisions are less likely to be affected by financial incentives for or against test or chemotherapy use. These tests are potentially costly, and may be marketed directly to patients, as well as physicians.[5,7] As genetic testing in cancer grows more common, healthcare systems need to systematically evaluate how consistently such tests are being used, and how much incremental benefit they add to baseline clinical practices.[8,9]

Breast cancer genetic testing provides a useful paradigm for evaluating the impact of such tests at a population level. Decisions about the use of adjuvant chemotherapy, for women with early-stage breast tumors that are estrogen or progesterone receptor positive (ER/PR+), can be especially difficult, as most will never experience a recurrence, even without adjuvant chemotherapy. Currently, several gene-expression profiling tests are being marketed to clinicians and patients as tools to enhance the accuracy of predicting recurrence risk and the likelihood of realizing benefit from adjuvant chemotherapy. The 21-gene Oncotype DX (Genomic Health, Inc, Redwood City, California) breast cancer assay has been validated in clinical trials to predict risk of distant recurrence in patients with early-stage, node-negative, ER/PR+, human epidermal growth factor receptor 2 negative (HER2–) cancers.[10-13] Guidelines for incorporating Oncotype DX testing into treatment decisions

Take-Away Points

In this retrospective cohort study, we evaluated the use of a multigene test that predicts recurrence risk in localized breast cancer, and associated trends in chemotherapy use in eligible patients.

- The multigene test was used in fewer than 1 in 3 eligible patients, with use plateauing in 2010 through 2012.
- Recurrence risk scores on the test were highly, but not perfectly, correlated with the use of chemotherapy.
- Introduction of the test was associated with a modest decrease in overall chemotherapy use.

were published in 2007[14,15]; however, little is known about how this test and other genomic tests are being incorporated into real-world oncology practice and how they affect patterns of care.

This study's overall objective was to assess how the 21-gene test is being used among patients with early-stage breast cancer in a large integrated health delivery system. Among patients who met current guidelines for use of this test, our aims were to: a) compare the demographic and clinical characteristics of patients who had the test with those who did not; b) describe chemotherapy use among women with test results that indicate low, intermediate, and high risk of recurrence; and c) evaluate whether the introduction of the test was associated with a change in chemotherapy use.

METHODS

Setting

Kaiser Permanente Northern California (KPNC) is a nonprofit integrated healthcare delivery system that currently provides care to more than 3.9 million members. Within KPNC, essentially all primary and specialty care, and the vast majority of emergency and hospital care, is delivered by providers working within a single care system for patients of a single health plan.[16]

Identification of Breast Cancers and Cancer Characteristics

The KPNC tumor registry—a contributor to the SEER program of cancer registries—was used to identify all female KPNC members diagnosed with invasive, nonmetastatic, incident breast cancer between September 1, 2005 (when significant use of Oncotype DX began at KPNC), and June 30, 2012. A member's first, newly diagnosed breast cancer during this period was included. The tumor registry includes patient age, sex, diagnosis date, tumor size, node involvement, ER/PR status, stage, and initial chemotherapy treatment. HER2 status was determined using the results of Immunohistochemistry and Fluorescence In Situ Hybridization tests.

In 2007, both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology included Oncotype DX testing in their guidelines.[14,15] Following NCCN guidelines, we selected women for whom Oncotype DX was to be considered: those with ER/PR+, HER2–, stage I and stage II breast cancers having primary tumors ≥0.51 cm with either no lymph node involvement or only ≤2 mm axillary node micro-metastases.[14] The Oncotype DX assay analyzes the expression of 21 genes to provide a Recurrence Score (RS) corresponding to the risk of distant recurrence at 10 years among tamoxifen-treated patients not treated with chemotherapy.[12,13] The RS is classified into 3 categories based on likelihood of distant recurrence: low risk (RS <18), intermediate risk (RS 18-30), and high risk (RS ≥31). Low RS has been shown to predict little benefit from chemotherapy, whereas high RS predicts greater benefit.[13] The routine approach in this medical group was to follow NCCN recommendations; thus, other genetic tests for breast cancer were not commonly used.

Due to the timing of SEER registry reporting requirements, there is some underascertainment of the chemotherapy treatment status in the tumor registry. As part of an ongoing prospective study of newly diagnosed cases of breast cancer,[17] a subset of cases were reviewed to validate the chemotherapy treatment status. Of 7004 eligible cancers, 62% were reviewed. Of 1071 patients validated to have used chemotherapy, 86.18% were correctly classified as such in the registry, and of 3240 patients validated not to have used chemotherapy, 99.97% were correctly classified in the registry. The chemotherapy status used was the validated one, if it existed; otherwise, the registry status was used.

Patient Characteristics

Patients were assigned to a census block group (defined by the US 2010 Census) based on their home address at the time of cancer diagnosis. Block group income and education were based on the 2006 to 2010 American Community Survey.[18,19] We used data from the year before the cancer diagnosis to create a modified Deyo version of the Charlson comorbidity index.[20] From administrative databases, we extracted (from the year before the cancer diagnosis) the following additional variables for each patient for use in the propensity score matching: primary medical center used for care, number of clinic visits and hospital days, and their associated cost.

Analyses

To identify the predictors of receiving 21-gene testing, we used logistic regression, in which receipt of the test was the dependent variable. Independent variables were calendar year of cancer diagnosis (as a categorical variable), age group (5 categories: aged <40, 40 to <50, 50 to <65, 65 to <75, and ≥75 years), race/ethnicity (Asian, black, white Hispanic, white non-Hispanic, and other/unknown), tumor size (3 categories: 0.5 cm to ≤1.0 cm, >1.0 cm to ≤2.0 cm, and >2.0 cm), comorbidity (3 categories: 0, 1-2, and ≥3 comorbidities), census block group median income, and proportion of adults in the block group with less than a high school degree.

To assess the potential impact of 21-gene testing on receipt of chemotherapy, we used 2 different analytic approaches. The first approach directly evaluated whether women who received the test were more or less likely to receive chemotherapy compared with women who were not tested. We ran a logistic regression in which the dependent variable was whether the woman was tested, and the independent variables were the same as those listed above, plus the following (to increase further the similarity of the matched cohorts): primary medical center for care, patient's age-squared (for potential nonlinear age effects), costs of clinic and hospital services, as well as the number of clinic visits and hospital days in the year before cancer diagnosis. Model calibration and discrimination were good (C statistic = 0.81; Hosmer-Lemeshow goodness of fit test: $P = .32$, with nonsignificance reflecting adequate fit). The resulting predicted probability of receiving the test was the patient's propensity score.

We selected patients who received the 21-gene test and matched them 1-to-1 to patients who were not tested. Matching was performed using the Mahalanobis metric matching within calipers, defined as one-fourth of the standard deviation of the logit of the propensity score.[21] Using this methodology, 93% (n = 1462) of tested women were matched to a nontested woman, and after matching, there were no significant differences between the cohorts with regard to the variables used in the propensity score calculation. However, women in the matched cohorts were younger and had fewer comorbidities than the general pool of women from whom they were drawn. This reflects the fact that among the entire cohort of patients with cancer, tested women tended to be different from nontested women.

Using the propensity-matched samples, we calculated the percent of women in each sample receiving chemotherapy, and the corresponding ratio of the odds of receiving chemotherapy among women tested, to the odds of receiving chemotherapy among matched women not tested. As a sensitivity analysis, the matched analysis was repeated among the subset of patients with validated chemotherapy use.

The second analytical approach was to treat the overall percent of women who received testing as a predictive variable for receiving chemotherapy. This approach is similar to "ecological" regression, wherein aggregates are used either in place of, or in addition to, individual-level predictors.[22] Unlike an interrupted time-series analysis in which differences before and after some change in practice are assessed, this approach does not require us to arbitrarily define time periods as "before" or "after" the introduction of the test, given that testing was phased in over time. We started with an analytic data set with 1 record per woman. For each calendar year and age group, we calculated the percent of women who received the test, and added this variable to the analytic data set. Thus, a woman diagnosed with cancer in 2011 who was aged 50 to <65 years, had a variable added to her record that reflected the percent of women in her age group in 2011 who were tested. Using these patient-level records, we ran a logistic regression in which receipt of chemotherapy was the dependent variable, and the independent variable of interest was the percent of women in the strata who were tested. The woman's own test status is not included in the model. Other independent variables included in the model were the same as those used in the model identifying predictors of testing. The results of this model were then used to predict the percent of women receiving chemotherapy, assuming 1 of 2 scenarios: 1) 0% of women in her age group and year were tested, and 2) 30% were tested (which was about the maximum percent of women who received the 21-gene test in any given year).

The first approach has been called an "individual-level analysis" and the second approach a "2-level analysis."[22] Each of these approaches has distinct advantages and disadvantages. The individual-level analysis has the advantage of directly measuring the relationship between the individual's use of the test and their use of chemotherapy, but does not account for certain aspects associated with self-selection of testing. For example, women with a strong predilection for or against chemotherapy may choose not to be tested—a problem similar to "confounding by indication." The 2-level "ecologic" analysis factors out some of the potential unmeasured confounders related to which women choose to be tested.[22] However, that approach is prone to bias if there are other unmeasured factors that may have increased or decreased use of chemotherapy at the same time as the increase in the use of testing.

RESULTS

Characteristics of Study Cohort

We identified 7004 women diagnosed with cancers meeting our inclusion criteria, who met guidelines for 21-gene testing (Table 1). The majority of women were under 65 years of age (57%) and 71% were non-Hispanic white. Three-fourths of cancers were stage I, and 70% of tumors were >1.0 cm in size. Overall, 21-gene testing was performed for 22% of women. In adjusted analyses, compared with women aged 50 to <65 years, women aged 40 to <50 years were more likely to be tested (OR, 1.22; 95% CI, 1.04-1.44), whereas women aged 65 to <75 years and ≥75 years were less likely to be tested (OR, 0.42; 95% CI, 0.36 to 0.49; and OR, 0.04; 95% CI, 0.02-0.06, respectively) (Table 2). Compared with women with tumors >2.0 cm, women with tumors 0.5 cm to ≤1.0 cm were less likely to be tested (OR, 0.51; 95% CI, 0.42-0.61), whereas women with tumors >1.0 to ≤2.0 cm were more likely to be tested (OR, 1.20; 95% CI, 1.03-1.40). Each $10,000 increase in block group median income was associated with increased odds of testing (OR, 1.05; 95% CI, 1.03-1.07).

Oncotype DX and Chemotherapy Use

Among women with 21-gene testing, 52%, 39%, and 9% had low-risk, intermediate-risk, and high-risk RS values, respectively (Table 3). Among women who had the test, a slightly higher percentage (26%) received chemotherapy compared with those who did not (22%; P <.01). Among women with low-, intermediate-, and high-risk RS, 8%, 40%, and 72%, respectively, received chemotherapy.

Between 2005 and 2012, the percent of eligible women receiving 21-gene testing rose from 8% to more than 25%, while the percent of women receiving chemotherapy decreased modestly from 26% to 22% (Figure 1). Younger women were much more likely to receive chemotherapy, and the 2 age groups with the most women receiving chemotherapy had the most pronounced downward trends in chemotherapy use from 2005 to 2012 (from 59% to 47% for those aged 40 to <50 years, and from 35% to 24% for those aged 50 to <65 years) (Figure 2).

Table 1. Characteristics of Patients Meeting NCCN Guidelines for Consideration of the 21-Gene Test for Breast Cancer Recurrence, and the Subgroup Who Received Testing (Kaiser Permanente Northern California, September 2005-June 2012)[a]

Characteristic	Patients With Breast Cancer, N (%)			% of All Patients Receiving 21-Gene Test[e]
	All[b]	Receiving 21-Gene Test[c]	Not Receiving 21-Gene Test[d]	
Total	7004 (100)	1567 (100)	5437 (100)	22
Age at diagnosis, years[f]				
<40	161 (2)	61 (4)	100 (2)	38
40-49	944 (13)	320 (20)	624 (11)	34
50-64	2922 (42)	875 (56)	2047 (38)	30
65-74	1856 (26)	293 (19)	1563 (29)	16
≥75	1121 (16)	18 (1)	1103 (20)	2
Race/ethnicity[f]				
Asian	967 (14)	277 (18)	690 (13)	29
Black	401 (6)	91 (6)	310 (6)	23
White, Hispanic	615 (9)	135 (9)	480 (9)	22
White, non-Hispanic	4983 (71)	1058 (68)	3925 (72)	21
Other or unknown	38 (1)	6 (<1)	32 (1)	16
Stage				
I	5226 (75)	1178 (75)	4048 (74)	23
II	1778 (25)	389 (25)	1389 (26)	22
Tumor size[f]				
>0.5 cm to ≤1.0 cm	2069 (30)	287 (18)	1782 (33)	14
>1.0 cm to ≤2.0 cm	3376 (48)	907 (58)	2469 (45)	27
>2.0 cm	1559 (22)	373 (24)	1186 (22)	24
Charlson comorbidity score[f]				
Low (0)	5111 (73)	1231 (79)	3880 (71)	24
Intermediate (1-2)	1682 (24)	313 (20)	1369 (25)	19
High (≥3)	211 (3)	23 (1)	188 (3)	11
Initial treatments[f]				
Chemotherapy	1600 (23)	410 (26)	1190 (22)	26
Radiation therapy	3463 (49)	825 (53)	2638 (49)	24
Hormone therapy	4374 (62)	1094 (70)	3280 (60)	25

NCCN indicates National Comprehensive Cancer Network.
[a]Among breast cancer cases meeting National Comprehensive Cancer Network criteria for consideration of the 21-gene test (Oncotype DX). See text for inclusion criteria.
[b]Denominator for percent is the number of patients with breast cancer in the study cohort (n = 7004).
[c]Denominator for percent is the number of patients with breast cancer receiving 21-gene test (n = 1567).
[d]Denominator for percent is the number of patients with breast cancer not receiving 21-gene test (n = 5437).
[e]Denominator is the number of patients with breast cancer in that demographic/clinical subgroup. For example, among the 161 women aged <40 in the cohort, 61 (38%) of them received the 21-gene test.
[f]Patients receiving 21-gene test were significantly different from those not receiving test at P ≤.05, unadjusted.

Table 2. Demographic and Clinical Predictors of Receiving the 21-Gene Test for Breast Cancer Recurrence (Kaiser Permanente Northern California, September 2005-June 2012)[a]

Characteristic	Adjusted OR of Being Tested vs Not Being Tested (95% CI)[b]
Year	
2005	0.87 (0.55-1.37)
2006	ref
2007	2.03 (1.52-2.70)[c]
2008	3.53 (2.68-4.64)[c]
2009	3.92 (2.98-5.15)[c]
2010	4.61 (3.53-6.03)[c]
2011	4.59 (3.52-5.98)[c]
2012	3.54 (2.63-4.77)[c]
Age at diagnosis, years	
<40	1.34 (0.94-1.89)
40-49	1.22 (1.04-1.44)[c]
50-64	ref
65-74	0.42 (0.36-0.49)[c]
≥75	0.04 (0.02-0.06)[c]
Race/ethnicity	
Asian	1.04 (0.88-1.23)
Black	0.95 (0.73-1.24)
Other or unknown	0.45 (0.18-1.11)
White, Hispanic	0.81 (0.65-1.02)
White, non-Hispanic	ref
Tumor size	
>0.5 cm to ≤1.0 cm	0.51 (0.42-0.61)[c]
>1.0 cm to ≤2.0 cm	1.20 (1.03-1.40)[c]
>2.0 cm	ref
Charlson comorbidity score	
Low (0)	1.35 (0.85-2.16)
Intermediate (1-2)	1.27 (0.79-2.05)
High (≥3)	ref
Census-block group characteristics	
Median income[d]	1.05 (1.03-1.07)[c]
Proportion of adults with less than high school degree	1.97 (0.99-3.90)

OR indicates odds ratio; ref, reference.
[a]Among breast cancer cases meeting National Comprehensive Cancer Network criteria for consideration of the 21-gene test (Oncotype DX) (n = 7004). See text for inclusion criteria.
[b]Odds ratios estimated using multivariate logistic regression.
[c]Statistically significant at $P \leq .05$.
[d]Results reflect odds for each increase of $10,000 in census block median income.

In analyses with individual-level propensity score matching (n = 2924), receipt of the 21-gene testing was associated with decreased odds of chemotherapy (OR, 0.74; 95% CI, 0.63-0.87), corresponding to a reduction in the percent of women receiving chemotherapy from 32.7% to 26.5%, or an absolute reduction of 6.2% (95% CI, 2.9%-9.5%). When including only women with validated chemotherapy treatment status, 21-gene testing was associated with lower odds of chemotherapy (OR, 0.64; 95% CI, 0.53-0.78) than in the primary analysis, corresponding to an absolute reduction of 9.5% (95% CI, 5.3%-13.6%). Among this matched cohort, women who had received Oncotype DX testing and went on to receive chemotherapy were older, and were more likely to have stage I cancer and smaller tumors, than women who had not received Oncotype DX testing and went on to receive chemotherapy.

In the 2-level multivariable (ecological) analysis, each 10% increase in the absolute percent of women tested was associated with a 0.92 decreased odds of chemotherapy, but this result was not statistically significant (95% CI, 0.83-1.03; $P = .14$). The point estimates of this model imply that 26% of women in the study would have received chemotherapy in the absence of any testing, while 23% would receive chemotherapy if 30% of women were tested.

DISCUSSION

This is among the first large investigations of the use and impact of the 21-gene test for breast cancer recurrence risk in a managed care population. In this integrated system, we found that although rates of use increased over time, only 20% to 25% of patients meeting guidelines received testing. In adjusted analyses, use of testing was differential by age, tumor size, and neighborhood-level income. Patterns of chemotherapy use were generally consistent with test results, with those having a low RS far less likely to have chemotherapy than those with a high RS. When used, the test was associated with a modest reduction in overall chemotherapy use.

The rates of testing we observed were similar to other reports from US populations,[2,4,5] including those of a large, for-profit oncology network.[23] One difference from past studies is that we found no racial/ethnic differences in use of the test. For example, Guth et al found that women treated at municipal hospitals—who were more likely to be of low income and nonwhite—were less likely to have the 21-gene test than socioeconomically similar women seen in tertiary care settings (3% vs 30%).[24] The fact that the test was fully covered by insurance in our setting removed patient-level financial barriers and may have mitigated racial/ethnic variation in test use. However, patients living in higher-income areas were more likely to have the test than those living in lower-income areas.

Table 3. Chemotherapy Treatment by Patient Group and 21-Gene Test Recurrence Score (Kaiser Permanente Northern California, September 2005-June 2012)[a]

Characteristic	Total Patients	Patients Receiving Chemotherapy, n (%)
All patients	7004	1600 (23)
Patients who did not have Oncotype DX testing	5437	1190 (22)
Patients who had Oncotype DX testing	1567	410 (26)
By RS[b]		
Low risk (RS ≤18)	820	68 (8)
Intermediate risk (RS = 18 to 30)	606	241 (40)
High risk (RS ≥31)	141	101 (72)

RS indicates Recurrence Score.
[a]Among breast cancer cases meeting National Comprehensive Cancer Network criteria for consideration of the 21-gene test (Oncotype DX). See text for inclusion criteria.
[b]Differences in the percent of patients receiving chemotherapy among the 3 Recurrence Score groups was statistically different at $P \leq 01$.

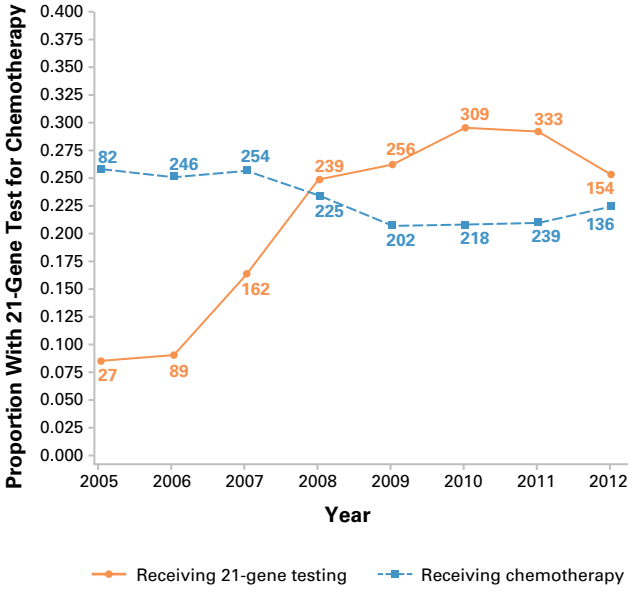
The other clinical and demographic correlates of non-use of 21-gene testing that we identified, such as smaller tumor size and older age, have also been observed in other settings.[23] For these subgroups, clinicians and/or their patients may have decided that chemotherapy was not indicated, so that testing would not change treatment decisions. Clinicians may also feel that standard clinicopathologic prognostic factors, existing decision tools (eg, Adjuvant!),[25] and/or a patient's health status or preferences are more important in treatment decision making than 21-gene test results.[26] However, it has been reported that, when obtained, the 21-gene results can change pre-testing treatment decisions in about 30% to 50% of cases.[6,27-29] A survey of KPNC oncologists, completed in spring 2015, suggests that among those patients who have the 21-gene test, the results cause changes in chemotherapy decisions in approximately 40%—and that these changes are equally divided among changes away from having chemotherapy and changes toward having chemotherapy (Lieu et al [unpublished data from a survey of 85 KPNC oncologists via mail and e-mail, as part of the overall project that produced this paper]).

This 21-gene test and other multigene tests have been promoted as likely to be cost-effective since test costs are expected to be offset by decreases in chemotherapy use among women with low recurrence risk, and, hence, low predicted benefits of chemotherapy.[3,6,30-32] In our matched analysis, we found that testing was associated with a 6% to 10% reduction in chemotherapy use. A recent meta-analysis estimated a somewhat higher percent reduction of 12%.[6] Our "ecologic" analysis indicated that an increase in testing in the KPNC setting, from 0% to 30%, resulted in approximately a 3% absolute decrease in the percent of women getting chemotherapy. The 2-level analysis is a more indirect (and conservative) approach, with fewer observations due to the summarized nature of the analysis, and, therefore, has less power. Nevertheless, the direction of the result was the same as that of the propensity score-matched analysis. Regardless of approach, our estimated reductions in chemotherapy were far lower than the 31% reduction in chemotherapy observed in a smaller study of a younger cohort in Ireland.[3] The lower reduction in chemotherapy we observed relative to other studies was most likely due to our patient population being older and having a lower baseline percent of women receiving chemotherapy, as well as a lower percentage of eligible women being tested, compared with the study from Ireland.

Limitations and Strengths

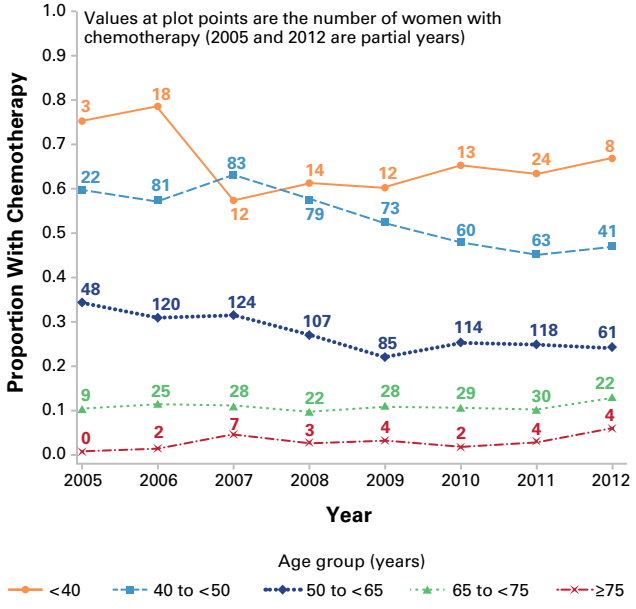
Our results should not be construed as suggesting that the 21-gene test is being underused, as the study only evaluated chemotherapy in relation to current levels of testing. Our results cannot be extrapolated to project whether, or by how much, chemotherapy use would de-

Figure 1. Proportion of 7004 Eligible Patients With Breast Cancer Receiving 21-Gene Testing and Chemotherapy by Year (Kaiser Permanente Northern California)



Solid line indicates receiving 21-gene testing; dotted line indicates receiving chemotherapy. Values at plot points are the number of women with 21-gene test or chemotherapy (2005 and 2012 are partial years).

Figure 2. Proportion of 7004 Patients With Breast Cancer Receiving Chemotherapy, by Age Group, Among Those Eligible for 21-Gene Testing (Kaiser Permanente Northern California)



crease if the test were used for a higher percentage of patients. The current level of testing may reflect clinicians' judgments that the nontested patients would not benefit from testing because the decision about chemotherapy is already clear in their cases.

Chemotherapy treatment decisions in our study were not always in accord with the RS. Among women with low RS, 8% received chemotherapy anyway, and 28% of those with high RS did not receive chemotherapy. Similar discordant use patterns were noted in a recent meta-analysis.[28] Our data did not enable us to determine the reasons for these conflicting choices; however, based on other reports,[23] it seems that discordant use patterns are not unexpected since multigene testing is only 1 factor in complex chemotherapy decisions, and test results are not an absolute mandate for or against chemotherapy. For instance, doctors may sometimes use the test to discourage a low-risk (based on tumor size, histology, grade) or unhealthy patient who wants chemotherapy from having it, or to encourage treatment in a high-risk, healthy patient who does not want it. In the latter situation, a patient may continue to refuse chemotherapy even after receiving a high-risk test result. Genomic testing may increase anxiety and impair decision making or results may be poorly understood.[33-36]

This study has many strengths, including its fully enumerated managed care population, inclusion of only those cases with clinical indications for 21-gene testing, and ability to relate test results to chemotherapy use. Although these findings from an integrated health plan population in California may not be representative of all practice settings, the testing and treatment patterns we found were remarkably similar to those reported from other settings.[2,23] This suggests that clinical norms, randomized controlled trial evidence, and national recommendations may be more important to physicians' ordering behavior than the costs of the test or who is covering those costs. That chemotherapy is sometimes discordant from therapy suggested by the RS indicates that patient factors may be as, or more important than the healthcare structure. These hypotheses will need to be tested explicitly in future research across diverse healthcare systems and populations.

CONCLUSIONS

Overall, this study suggests that in a large integrated healthcare system, the 21-gene test is used in a minority of eligible patients, but when used, it is leading to clinically appropriate patterns of chemotherapy use. Optimizing the benefit and efficiency of this and other genomic tests for cancer patients will require additional research on the factors that drive test use and subsequent decisions about chemotherapy.

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